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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
07/07/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/756,153	JOHNSON ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48,50,56,58 and 61-72* is/are pending in the application.

4a) Of the above claim(s) *1,2,7,9-22,24-48 and 50* is/are withdrawn from consideration.

5)☒ Claim(s) *56* is/are allowed.

6)☒ Claim(s) *3-6,8,23,58 and 61-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response and amendments received April 2, 2009 are acknowledged.

Claims 49, 51-55, 57, 59, and 60 have been canceled.
Claims 1, 3-5, 7-9, 13, 15, 17, 18, 23, 32, 35, 56, and 58 have been amended.
Claims 61-72 have been added.
Claims 1-48, 50, 56, 58, and 61-72 are pending in the instant application.
Claims 1, 2, 7, 9-22, 24-48, and 50 stand withdrawn from consideration as being drawn to a nonelected invention. See 37 CFR 1.142(b) and MPEP § 821.03, for reasons of record set forth in restriction requirement mailed July 28, 2008.

Claims 3-6, 8, 23, 56, 58, and 61-72 are under examination in this office action.

Specification

2. The title and abstract are objected to for not clearly indicating the subject matter that is being examined in this instant application. Specific mention of $Fc_{\gamma}RIIB$ is suggested as part of an appropriate amendment to overcome this objection.

Applicant has acknowledged this objection but believes it to be premature since no subject matter has been indicated as allowable, And thus has asked that the objection be held in abeyance.

Since applicant has not amended either the title or abstract, the objection is maintained.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

> art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. The rejection of claims 3-6, 23, and 58 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement has been withdrawn in view of applicant's claim amendments received April 2, 2009.

Specifically, the claims have been amended to remove the recitation that the claimed fusion proteins "do not bind any FcγR".

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. The rejection of claim 56 under 35 U.S.C. 102(b) as being anticipated by Maddon et al. (US Patent 6,034,223) has been withdrawn in view of applicant's claim amendments received April 2, 2009 which indicate that the claimed polypeptide must comprise the entirety of SEQ ID NO:42. Thus, the claim no longer reads on fragments of SEQ ID NO:42 and the rejection has been withdrawn.

7. The rejection of claim 56 under 35 U.S.C. 102(b) as being anticipated by Sondermann et al. (WO 00/32767, of record as B9 on the 8/28/08 IDS) has been withdrawn in view of applicant's claim amendments received April 2, 2009 which indicate that the claimed polypeptide must comprise the entirety of SEQ ID NO:42. Thus, the claim no longer reads on fragments of SEQ ID NO:42 and the rejection has been withdrawn.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. The rejection of claims 8 and 56 under 35 U.S.C. 103(a) as being unpatentable over Presta et al. (US Patent 6,911,321) in view of Allaway et al. (US Patent 5,817,767) has been withdrawn in view of applicant's claim amendments received April 2, 2009.

Specifically, claim 8 has been amended to add the new limitation that the Fc domain comprises a mutation that modulates effector function, and claim 56 has been amended such that it no longer reads on fragments of the fusion protein of SEQ ID NO:42.

10. The rejection of claims 8 and 56 under 35 U.S.C. 103(a) as being unpatentable over Sondermann et al. (WO 00/32767, of record as B9 on the 8/28/08 IDS) in view of Ashkenazi et al. (Curr Opin Immunol, 1997, 9:195-200) and in view of Allaway et al. (US Patent 5,817,767) has been withdrawn in view of applicant's claim amendments received April 2, 2009.

Specifically, claim 8 has been amended to add the new limitation that the Fc domain comprises a mutation that modulates effector function, and claim 56 has been amended such that it no longer reads on fragments of the fusion protein of SEQ ID NO:42.

Claim Objections

11. The objection to claim 49 has been rendered moot by its cancellation as per applicant's amendments received April 2, 2009.

Applicant's claim amendments received April 2, 2009 have overcome all prior grounds of rejection. However, these same claim amendments have raised new issues necessitating the following new grounds of rejection.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 3-6, 8, 23, 65-72 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant has amended the independent claims to recite that the "Fc region comprises one or more amino acid modifications that modulate one or more effector functions of the Fc region". "Modulation" encompasses the diametrically opposed activities of increasing and decreasing. Also, as is disclosed in the specification, there are numerous effector functions, and the sequences within the Fc region which are responsible for such functions, for example binding to C1q, differ from the sequences which give rise to other functions, such as binding to FcRn. Additionally, different Fc regions naturally have different effector functions (compare IgE and IgG Fc), such that the naturally occurring sequence variations between IgE and IgG naturally "modulate" their effector function with respect to one another. Applicant's arguments appear to indicate that applicant intends on the newly presented language to read on point mutations introduced by way of genetic engineering, but the claims encompass more

than non-naturally occurring Fc domains. Given the ambiguous language of the claims as they relate to the nature of the "modifications" as well as the properties that are "modulated", the metes and bounds of the instant claimed invention are not known. Amending the claims to incorporate specific effector functions, Fc isotypes, and mutated positions as is done in dependent claims is one way to obviate this part of the rejection.

Additionally, claims 65-72 all recite "position 297" but the independent claims are not limited to a single sequence. Thus, reciting that position 297 is mutated in the absence of a specific sequence used to establish the numbering convention makes the claim indefinite. Amending the claims to recite a specific sequence by SEQ ID number that is used to establish positions or amending the claims to recite that the numbering is based upon the EU index are possible ways to obviate this part of the rejection.

14. Claim 58 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claim recites isolated polypeptides which are at least 75% homologous to the polypeptide of SEQ ID NO:42. SEQ ID NO:42 is an immunoadhesin which comprises the extracellular domain of human FcγRIIB. The claimed polypeptides are also recited as having the same binding and effector activity as SEQ ID NO:42. The specification discloses in the working examples that SEQ ID NO:42 has a longer half-life in vivo as compared to soluble FcγRIIB which lacks an Fc domain, and that SEQ ID NO:42 is protective in mouse models of ITP and autoimmune hemolytic anemia as compared to untreated animals. No data is presented concerning C1q binding, CDC activity, ADCC activity, or affinity binding measurements for interactions with the various types of FcγR receptors. No data is presented concerning administration of an FcγRIIB-Fc construct without mutations such that comparisons can be made to differentiate

effects due to the presence of the Fc tail in general as compared with the presence of the deglycosylated version comprising a mutation (which is SEQ ID NO:42).

The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, January 5, 2001, see especially page 1106 column 3).

In The Regents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412) 19 F. 3d 1559, the court noted: "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material."

The court has further stated that "Adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." Id. at 1566, 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). Also see Enzo-Biochem v. Gen-Probe 01-1230 (CAFC 2002).

As discussed above, the specification does not clearly indicate what functional activities of SEQ ID NO:42 are, or how its effector activities differ from similar polypeptides which comprise N-linked glycosylation at position 297 in the Fc effector domain. Skolnick et al. (Trends in Biotechnology, 18(1):34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (see particularly the Abstract and the section titled Sequence-based approaches to function prediction on page 34). Even in situations where there is some confidence of a similar overall structure between two sequences, only experimental research can confirm the artisan's best guess as to the function of the structurally related sequence (see in particular the Abstract and Box 2 on page 36). The complexity of the problem of assigning function based on homology rises as the percent similarity or identity falls (see Whisstock et al., Quarterly Reviews of Biophysics, 2003, 36:307-340, particularly the sentence that spans pages 321 and 323). Note that the instant claims recite homology of at least 75%, but the standards used to define what substitutions are or are not considered homologous do not appear to be defined by the instant specification. Without such information, a skilled artisan would not know by simple inspection if any given polypeptide sequence does or does not meet the threshold for "homology" since the substitutions permitted by such language are undefined. This problem is compounded by the fact that as detailed above, the “effector functions” present in SEQ ID NO:42 are not thoroughly disclosed. As such, it does not appear that applicant has established a correlation between the recited level of sequence homology and maintenance of the effector functions of SEQ ID NO:42.

Therefore, it appears that the broad genus of polypeptides claimed by applicant lacks adequate written description because there does not appear to be adequate correlation between structure and function excepting for the polypeptide of SEQ ID NO:42. As such a skilled artisan would reasonably conclude that applicant was not in possession of the claimed genus of polypeptides at the time the application was filed.

15. Claims 3-6, 8, 23, and 61-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,911,321 (of record) in view of Allaway et al. (US Patent 5,817,767, of record) and in view of US Patent 6,737,056, newly presented.

The '321 patent discloses fusion polypeptides comprising $Fc_{\gamma}RIIB$ joined to the Fc portion of an immunoglobulin (see entire document, particularly lines 50-60 of column 4, columns 9 and 10, columns 23-25, and most particularly lines 16-18 of column 25). It is also disclosed that soluble molecules comprising Fc receptors are to be used as therapeutics (see particularly column 13). This disclosure differs form the instant invention in that the '321 patent does not disclose that the immunoglobulin isotype is to be IgG2, nor does it disclose specific mutations that are made in the Fc domain to increase effector activity.

Allaway et al. disclose that fusion constructs wherein a heterologous molecule is joined to IgG2 enjoy the advantages of reduced potential immunogenicity since there is minimal allotypic variation in human IgG2 as compared to other isotypes (see entire document, particularly lines 60-67 of column 2).

The '056 patent discloses that the Fc domain of antibodies and immunoadhesins can be mutated to alter effector functions (see entire document, particularly the abstract and column 4). It further discloses that removing the N-linked glycosylation site at position 297 provides the advantage of reducing binding of the Fc domain to all $Fc\gamma Rs$ (see particularly Table 2 beginning in column 20), with the preferred substitution being to change the asparagine (N) to glutamine (Q) as detailed in Table 1 (column 20, and also lines 40-67 of column 25).

Therefore, the fusion polypeptides of the instant claimed invention would have been obvious to a person of ordinary skill in the art at the time the invention was made. A person of ordinary skill in the art would have been motivated to make the fusion constructs of the '321 patent comprising an IgG2 isotype to gain the advantage of reduced immunogenicity as disclosed by Allaway et al. and comprising a mutation at position 297 in the Fc domain to gain the advantage of decreased effector function as disclosed by the '056 patent.

16. Claims 3-6, 8, 23, and 61-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sondermann et al. (WO 00/32767, of record as B9 on the 8/28/08 IDS) in view of Ashkenazi et al. (Curr Opin Immunol, 1997, 9:195-200, of record) in view of Allaway et al. (US Patent 5,817,767, of record) and in view of US Patent 6,737,056, newly presented.

Sondermann et al. disclose soluble forms of human $Fc_{\gamma}RIIB$ (see entire document, particularly example 1 beginning on page 17). It is further disclosed that these soluble forms are to be administered in pharmaceutical compositions to patients (see particularly pages 8-9). This disclosure differs from the claimed in that fusion proteins comprising $Fc_{\gamma}RIIB$ joined to IgG2 are not disclosed, nor are fusion proteins comprising mutated Fc effector domains disclosed.

Ashkenazi et al. discloses that the administration of soluble therapeutic polypeptides as fusion molecules with the Fc domain of an immunoglobulin (aka immunoadhesins) enjoy the advantage of increased in vivo half-life as compared to the starting therapeutic polypeptide, and that such molecules have a further advantage of being easy to purify due to the Fc domain (see entire document, particularly the right column of page 195 and the left column of page 196). It is further disclosed that any human Fc domain can be used to make an immunoadhesin, and that the presence of the Fc domain makes such molecules dimeric (ibid. and Figure 1).

Allaway et al. disclose that fusion constructs wherein a heterologous molecule is joined to IgG2 enjoys the advantages of reduced potential immunogenicity since there is minimal allotypic variation in human IgG2 as compared to other isotypes (see entire document, particularly lines 60-67 of column 2).

The ‘056 patent discloses that the Fc domain of antibodies and immunoadhesins can be mutated to alter effector functions (see entire document, particularly the abstract and column 4). It further discloses that removing the N-linked glycosylation site at position 297 provides the advantage of reducing binding of the Fc domain to all $Fc\gamma Rs$ (see particularly Table 2 beginning in column 20), with the preferred substitution being

to change the asparagine (N) to glutamine (Q) as detailed in Table 1 (column 20, and also lines 40-67 of column 25).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to make the soluble $Fc_{\gamma}RIIB$ molecules of Sondermann et al. into immunoadhesins to gain the advantages of increased in vivo half-life and ease of purification as disclosed by Ashkenazi et al. A person of ordinary skill in the art would have been further motivated to select IgG2 as the isotype to be used in the immunoadhesin since immunoadhesins comprising IgG2 are less immunogenic than other human isotypes as was disclosed by Allaway et al. The ordinary artisan would also have been motivated to make immunoadhesins which comprise a mutation at position 297 in the Fc domain to gain the advantage of decreased effector function as disclosed by the '056 patent.

17. Claim 56 is allowable.

18. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is (571)272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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